CLAIMS

1. A substantially pure preparation of a plasmin inhibitor characterised in that it is a single stage competitive inhibitor of plasmin.
2. The plasmin inhibitor of claim 1 further characterised in that it has a dissociation constant for plasmin in the range of from $1x10^{-8}$ M^{-1} to $1x10^{-10}$ M^{-1}.
3. The plasmin inhibitor of claim 1 further characterised in that it has a dissociation constant for plasmin in the range of from $5x10^{-8}$ M^{-1} to $8x10^{-9}$ M^{-1}.
4. The plasmin inhibitor of claim 1 further characterised in that it has a dissociation constant for plasmin in the range of from $1x10^{-9}$ M^{-1} to $5x10^{-9}$ M^{-1}.
5. The plasmin inhibitor of claim 1 further characterised in that it has a dissociation rate constant for plasmin in the range of from $4x10^{-5}$ sec^{-1} M^{-1} to $5x10^{-7}$ sec^{-1} M^{-1}.
6. The plasmin inhibitor of claim 1 further characterised in that it has a dissociation rate constant for plasmin in the range of from $1x10^{-6}$ sec^{-1} M^{-1} to $1x10^{-7}$ sec^{-1} M^{-1}.
7. The plasmin inhibitor of claim 1 further characterised in that it has a dissociation rate constant for plasmin in the range of from $2x10^{-6}$ sec^{-1} M^{-1} to $9x10^{-6}$ sec^{-1} M^{-1}.
8. The plasmin inhibitor of claim 1 comprising a polypeptide selected from the group consisting of:

   (a). Lys-Asp-Arg-Pro-Asp-Phe-Cys-Glu-Leu-Pro-Ala-Asp-Thr-Gly-Pro-Cys-Arg-Val-Arg-Phe-Pro-Ser-Phe-Tyr-Tyr-Asn-Pro-Asp-Glu-Lys-Lys-Cys-Leu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Ala-Asn-Asn-Ph-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:2];

(b). Lys-Asp-Arg-Pro-Glu-Leu-Cys-Glu-Leu-Pro-Pro-Asp-Thr-Gly-Pro-Cys-Arg-Val-Arg-Phe-Pro-Ser-Phe-Tyr-Tyr-Asn-Pro-Asp-Glu-Gln-Lys-Cys-Leu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:4];

(c). Lys-Asp-Arg-Pro-Asn-Phe-Cys-Lys-Leu-Pro-Ala-Glu-Thr-Gly-Arg-Cys-Asn-Ala-Lys-Ile-Pro-Arg-Phe-Tyr-Tyr-Asn-Pro-Arg-Gln-His-Gln-Cys-Ile-Glu-Phe-Leu-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Lys-Thr-Ile-Lys-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:6];

(d). Lys-Asp-His-Pro-Lys-Phe-Cys-Glu-Leu-Pro-Ala-Glu-Thr-Gly-Ser-Cys-Lys-Gly-Asn-Val-Pro-Arg-Phe-Tyr-Tyr-Asn-Ala-Asp-His-His-Gln-Cys-Leu-Lys-Phe-Ile-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Lys-Thr-Ile-Glu-Glu-Gly-Lys-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:8];

(e). Lys-Asp-Arg-Pro-Lys-Phe-Cys-Glu-Leu-Leu-Pro-Asp-Thr-Gly-Ser-Cys-Glu-Asp-Phe-Thr-Gly-Ala-Phe-His-Tyr-Ser-Thr-Arg-Asp-Arg-Glu-CysIle-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:10]; and

(f). Lys-Asp-Arg-Pro-Lys-Phe-Cys-Glu-Leu-Pro-Ala-Asp-Ile-Gly-Pro-Trp-Asp-Asp-Phe-Thr-Gly-Ala-Phe-His-Tyr-Ser-Pro-Arg-Glu-His-Glu-Cys-Ile-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Lys-Gly-Asn-Ala-Asn-Asn-Phe-Asn-Thr-Gln-Glu-Gln-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:12];

(g). a biologically-active fragment of any one of SEQ ID NO:2, 4, 6, 8, 10 and 12; and

(h). a variant or derivative of any of the foregoing polypeptides of fragments thereof.

9. The plasmin inhibitor of claim 8 wherein said variant has the general formula: KDZPZŸCZLBBZBGXCZXXXBXFÃYXBZZZZCBZFBYGGCXBNANNF XTXEECESTCAA (I), wherein: -

X is any amino acid;

Ÿ is a hydrophobic amino acid;

Ã is an aromatic amino acid;

Z is K, R, H, D, E, Q or N; and

B is a neutral amino acid, or P, A, G, S, T, V or L.

10. The plasmin inhibitor of claim 9, wherein the Z at position 3 is H or R.

11. The plasmin inhibitor of claim 9, wherein the Z at position 5 is K, N, E or D.

12. The plasmin inhibitor of claim 9, wherein the Ÿ at position 6 is F or L.

13. The plasmin inhibitor of claim 9, wherein the Z at position 8 is E or K.

14. The plasmin inhibitor of claim 9, wherein the B at position 10 is P or L.

15. The plasmin inhibitor of claim 9, wherein the B at position 11 is P or A.

16. The plasmin inhibitor of claim 9, wherein the Z at position 12 is E or D.

17. The plasmin inhibitor of claim 9, wherein the B at position 13 is T or I.

18. The plasmin inhibitor of claim 9, wherein the X at position 15 is P, S or R.

19. The plasmin inhibitor of claim 9, wherein theZ at position 17 is K, N, E, D or R.

20. The plasmin inhibitor of claim 9, wherein the X at position 18 is D, G, A or V.

21. The plasmin inhibitor of claim 9, wherein the X at position 19 is F, N, K or R.

22. The plasmin inhibitor of claim 9, wherein theX at position 20 is T, P, F or I.

23. The plasmin inhibitor of claim 9, wherein the B at position 21 is G, V or P.

24. The plasmin inhibitor of claim 9, wherein the X at position 22 is A, S or R.

25. The plasmin inhibitor of claim 9, wherein the Ã at position 24 is Y or H.

26. The plasmin inhibitor of claim 9, wherein the X at position 26 is S or N.

27. The plasmin inhibitor of claim 9, wherein the B at position 27 is P, A or T.

28. The plasmin inhibitor of claim 9, wherein the Z at position 28 may be D or R.

29. The plasmin inhibitor of claim 9, wherein the Z at position 29 is E, D, H or Q.

30. The plasmin inhibitor of claim 9, wherein the Z at position 30 is H, K, R or Q.

31. The plasmin inhibitor of claim 9, wherein the Z at position 31 is K, Q or E.

32. The plasmin inhibitor of claim 9, wherein the B at position 33 is L or I.

33. The plasmin inhibitor of claim 9, wherein the Z at position 34 is E or K.

34. The plasmin inhibitor of claim 9, wherein the B at position 36 is L or I.

35. The plasmin inhibitor of claim 9, wherein the X at position 41 is E, G or K.

36. The plasmin inhibitor of claim 9, wherein the B at position 42 is C or G.

37. The plasmin inhibitor of claim 9, wherein the X at position 48 is K, N or I.

38. The plasmin inhibitor of claim 9, wherein the X at position 50 is K, Q or I.

39. The plasmin inhibitor of claim 8, wherein the polypeptide comprises a leader peptide comprising the sequence:- Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser [SEQ ID NO:14], or a biologically-active fragment thereof, or variant or derivative of these.

40. The plasmin inhibitor of claim 39, wherein the polypeptide is selected from the group consisting of:-

(a) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Asp-Phe-Cys-Glu-Leu-Pro-Ala-Asp-Thr-Gly-Pro-Cys-Arg-Val-Arg-Phe-Pro-Ser-Phe-Tyr-Tyr-Asn-Pro-Asp-Glu-Lys-Lys-Cys-Leu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:16];

(b) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Glu-Leu-Cys-Glu-Leu-Pro-Pro-Asp-Thr-Gly-Pro-Cys-Arg-Val-Arg-Phe-Pro-Ser-Phe-Tyr-Tyr-Asn-Pro-Asp-Glu-Gln-Lys-Cys-Leu-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Glu-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:18];

(c) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Asn-Phe-Cys-Lys-Leu-Pro-Ala-Glu-Thr-Gly-Arg-Cys-Asn-Ala-Lys-Ile-Pro-Arg-Phe-Tyr-Tyr-Asn-Pro-Arg-Gln-His-Gln-Cys-Ile-Glu-Phe-Leu-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Lys-Thr-Ile-Lys-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:20];

(d) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-His-Pro-Lys-Phe-Cys-Glu-Leu-Pro-Ala-Glu-Thr-Gly-Ser-Cys-Lys-Gly-Asn-Val-Pro-Arg-Phe-Tyr-Tyr-Asn-Ala-Asp-His-His-Gln-Cys-Leu-Lys-Phe-Ile-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Lys-Thr-Ile-Glu-Glu-Gly-Lys-Ser-Thr-Cys-Ala-Ala [SEQ ID NO:22];

(e) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Lys-Phe-Cys-Glu-Leu-Leu-Pro-Asp-Thr-Gly-Ser-Cys-Glu-Asp-Phe-Thr-Gly-Ala-Phe-His-Tyr-Ser-Thr-Arg-Asp-Arg-Glu-Cys-Ile-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Gly-Gly-Asn-Ala-Asn-Asn-Phe-Ile-Thr-Lys-Glu-Glu-Cys-Glu-Ser-Thr-Cys-Ala-Ala; [SEQ ID NO:24]; and

(f) Met-Ser-Ser-Gly-Gly-Leu-Leu-Leu-Leu-Leu-Gly-Leu-Leu-Thr-Leu-Trp-Glu-Val-Leu-Thr-Pro-Val-Ser-Ser-Lys-Asp-Arg-Pro-Lys-Phe-Cys-Glu-Leu-Pro-Ala-Asp-Ile-Gly-Pro-Trp-Asp-Asp-Phe-Thr-Gly-Ala-Phe-His-Tyr-Ser-Pro-Arg-Glu-His-Glu-Cys-Ile-Glu-Phe-Ile-Tyr-Gly-Gly-Cys-Lys-Gly-Asn-Ala-Asn-Asn-Phe-Asn-Thr-Gln-Glu-Gln-Cys-Glu-Ser-Thr-Cys-Ala-Ala; [SEQ ID NO:26].

41. An isolated polynucleotide encoding the polypeptide of claim 8.

42. An isolated polynucleotide selected from the group consisting of:-

(a) AAGGACCGTCCGGATTTCTGTGAACTGCCTGCTGACACCGGACC

ATGTAGAGTCAGATTCCCATCCTTCTACTACAACCCAGATGAAAA
AAAGTGCTAGAGTTTATTTATGGTGGATGCGAAGGGAATGCTAA
CAATTTTATCACCAAAGAGGAATGCGAAAGCACCTGTGCTGCCT
GA [SEQ ID NO:1];

(b) AAGGACCGTCCAGAGTTGTGTGAACTGCCTCCTGACACCGGACC
ATGTAGAGTCAGATTCCCATCCTTCTACTACAACCCAGATGAACA
AAAATGCCTAGAGTTTATTTATGGTGGATGCGAAGGGAATGCTA
ACAATTTTATCACCAAAGAGGAATGCGAAAGCACCTGTGCTGCC
TGA [SEQ ID NO:3];

(c) AAGGACCGTCCAAATTTCTGTAAACTGCCTGCTGAAACCGGACG
ATGTAATGCCAAAATCCCACGCTTCTACTACAACCCACGTCAAC
ATCAATGCATAGAGTTTCTCTATGGTGGATGCGGAGGGAATGCT
AACAATTTTAAGACCATTAAGGAATGCGAAAGCACCTGTGCTGC
ATGA [SEQ ID NO:5];

(d) AAGGACCATCCAAAATTCTGTGAACTCCCTGCTGAAACCGGATC
ATGTAAAGGCAACGTCCCACGCTTCTACTACAACGCAGATCATC
ATCAATGCCTAAAATTTATTTATGGTGGATGTGGAGGGAATGCTA
ACAATTTTAAGACCATAGAGGAAGGCAAAAGCACCTGTGCTGCC
TGA [SEQ ID NO:7];

(e) AAGGACCGTCCAAAATTCTGTGAACTGCTTCCTGACACCGGATC
ATGTGAAGACTTTACCGGAGCCTTCCACTACAGCACACGTGATC
GTGAATGCATAGAGTTTATTTATGGTGGATGCGGAGGGAATGCT
AACAATTTTATCACCAAAGAGGAATGCGAAAGCACCTGTGCTGC
CTGA [SEQ ID NO:9];

(f) AAGGACCGTCCAAAGTTCTGTGAACTGCCTGCTGACATCGGACC
ATGGGATGACTTTACCGGAGCCTTCCACTACAGCCCACGTGAAC
ATGAATGCATAGAGTTTATTTATGGTGGATGCAAAGGGAATGCT

AACAACTTTAATACCCAAGAGCAATGCGAAAGCACCTGTGCTGC CTGA [SEQ ID NO:11];

(g) a polynucleotide fragment of any one of SEQ ID NOS 1, 3, 5, 7, 9 and 11, wherein said polynucleotide fragment encodes a biologically-active fragment of any one of SEQ ID NO:2, 4, 6, 8, 10 and 12; and

(h) a polynucleotide homologue of any of the foregoing sequences.

43. The polynucleotide of claim 42 further comprising a nucleotide sequence encoding a leader peptide.

44. The polynucleotide of claim 43, wherein the nucleotide sequence comprises the sequence:-

ATGTCTTCTGGAGGTCTTCTTCTCCTGCTGGGACTCCTCACCCTCTG GGAGGTGCTGACCCCCGTCTCCAGC [SEQ ID NO:13] or a biologically active fragment thereof, or a polynucleotide homologue of these.

45. The polynucleotide of claim 43, wherein said polynucleotide is selected from the group consisting of:-

(a) ATGTCTTCTGGAGGTCTTCTTCTCCTGCTGGGACTCCTCACCCTCT GGGAGGTGCTGACCCCCGTCTCCAGCAAGGACCGTCCGGATTTC TGTGAACTGCCTGCTGACACCGGACCATGTAGAGTCAGATTCCC ATCCTTCTACTACAACCCAGATGAAAAAAAGTGCCTAGAGTTTAT TTATGGTGGATGCGAAGGGAATGCTAACAATTTTATCACCAAAG AGGAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:15];

(b) ATGTCTTCTGGAGGTCTTCTTCTCCTGCTGGGACTCCTCACCCTCT GGGAGGTGCTGACCCCCGTCTCCAGCAAGGACCGTCCAGAGTTG TGTGAACTGCCTCCTGACACCGGACCATGTAGAGTCAGATTCCCA TCCTTCTACTACAACCCAGATGAACAAAAATGCCTAGAGTTTATT TATGGTGGATGCGAAGGGAATGCTAACAATTTTATCACCAAAGA GGAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:17];

(c) ATGTCTTCTGGAGGTCTTCTTCTCCTGCTGGGACTCCTCACCCTCT
GGGAGGTGCTGACCCCCGTCTCCAGCAAGGACCGTCCAAATTTC
TGTAAACTGCCTGCTGAAACCGGACGATGTAATGCCAAAATCCC
ACGCTTCTACTACAACCCACGTCAACATCAATGCATAGAGTTTCT
CTATGGTGGATGCGGAGGGAATGCTAACAATTTTAAGACCATTA
AGGAATGCGAAAGCACCTGTGCTGCATGA [SEQ ID NO:19];

(d) ATGTCTTCTGGAGGTCTTCTTCTCCTGCTGGGACTCCTCACCCTCT
GGGAGGTGCTGACCCCCGTCTCCAGCAAGGACCATCCAAAATTC
TGTGAACTCCCTGCTGAAACCGGATCATGTAAAGGCAACGTCCC
ACGCTTCTACTACAACGCAGATCATCATCAATGCCTAAAATTTAT
TTATGGTGGATGTGGAGGGAATGCTAACAATTTTAAGACCATAG
AGGAAGGCAAAAGCACCTGTGCTGCCTGA [SEQ ID NO:21];

(e) ATGTCTTCTGGAGGTCTTCTTCTCCTGCTGGGACTCCTCACCCTCT
GGGAGGTGCTGACCCCCGTCTCCAGCAAGGACCGTCCAAAATTC
TGTGAACTGCTTCCTGACACCGGATCATGTGAAGACTTTACCGGA
GCCTTCCACTACAGCACACGTGATCGTGAATGCATAGAGTTTATT
TATGGTGGATGCGGAGGGAATGCTAACAATTTTATCACCAAAGA
GGAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:23];

(f) ATGTCTTCTGGAGGTCTTCTTCTCCTGCTGGGACTCCTCACCCTCT
GGGAGGTGCTGACCCCCGTCTCCAGCAAGGACCGTCCAAAGTTC
TGTGAACTGCCTGCTGACATCGGACCATGGGATGACTTTACCGG
AGCCTTCCACTACAGCCCACGTGAACATGAATGCATAGAGTTTAT
TTATGGTGGATGCAAAGGGAATGCTAACAACTTTAATACCCAAG
AGCAATGCGAAAGCACCTGTGCTGCCTGA [SEQ ID NO:25]; and

(g) GGAGCTTCATCATGTCTTCTGGAGGTCTTCTTCTCCTGCTGGGAC
TCCTCACCCTCTGGGAGGTGCTGACCCCCGTCTCCAGCAAGGACC
GTCCAGAGTTGTGTGAACTGCCTCCTGACACCGGACCATGTAGA

GTCAGATCCCCATCCTTCTACTACAACCCAGATGAACAAAAATG
CCTAGAGTTTATTTATGGTGGATGCGAAGGGAATGCTAACCAATT
TTATCACCAAAGAGGAATGCGAAAGCACCTGTGCTGCCTGAATG
AGGAGACCCTCCTGGATTGGATCGACAGTTCCAACTTGACCCAA
AGACCCTGCTTCTGCCCTGGACCACCCTGGACACCCTTCCCCCAA
ACCCCACCCTGGACTAATTCCTTTTCTCTGCAATAAAGCTTTGGT
TCCAGCT [SEQ ID NO:43]

46. A pharmaceutical composition for alleviating blood loss in a patient, said composition comprising the polypeptide of claim 8 and a pharmaceutically acceptable carrier.

47. A method for alleviating blood loss comprising the step of administering to a patient in need of such treatment a therapeutically effective dosage of the polypeptide of claim 8 in combination with a pharmaceutically acceptable carrier.

48. An anti-tumour agent comprising the polypeptide of claim 8 conjugated with an anti-fibrin antibody.